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Multiadaptive Plan (MAP) IMRT to Accommodate Independent Movement of the Prostate and Pelvic Lymph Nodes

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14. ABSTRACT

We found that the bi-directional prostate shifts, particular in anterior-posterior and superior-inferior directions, must be considered with the multiple adaptive plan (MAP) strategy. With this strategy, the verification plans calculated with daily MV-CBCT achieved similar dose coverage for the prostate and pelvic lymph nodes while adequate protecting the rectum and bladder. Furthermore, computer-assisted, atlas-based segmentation can improve consistency and efficiency in delineating volumes of the prostate and pelvic lymph nodes. Our future study will investigate whether the MLC-shifting strategy can effectively produce multiple plans for the multiple adaptive plan strategy and improve clinical work efficiency.

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Introduction

It is estimated that 40% or more of patients with intermediate to high risk prostate cancer will relapse locally and systemically within five years after definitive radiotherapy. We hypothesize that this high rate of failure is partly due to under-irradiation of the pelvic lymph nodes. One of the challenges to using IMRT in concurrent treatment of the prostate and the pelvic lymph nodes is the independent movement of the prostate relative to the lymph nodes, rendering the conventional iso-center shifting method of tracking prostate movement inadequate. The purpose of this research is to develop a novel method using multi-adaptive plan (MAP) IMRT to accommodate independent movement of the two targeted tumor volumes. In order to evaluate effectiveness of the MAP IMRT approach, we first establish a baseline benchmark by creating a set of ideal IMRT plans for each patient based on the daily acquired mega-voltage or kilo-voltage cone beam CT, which represents the ideal case of daily on line treatment planning. Based on this established benchmark, we can further evaluate two adaptive strategies: strategy A creates a set of IMRT plans individually optimizing on a series of possible prostate positions in the planning CT; and strategy B creates a set of multi-adaptive plans by dynamically adjusting the radiation apertures to accommodate the daily position of the prostate.

Body

(a) Obtain a new IRB approvals from Cleveland Clinic

After change of the research location from University of California-San Francisco (UCSF) to Cleveland Clinic, where the PI is currently located, the PI and her co- investigators spent another 6 months to establish a new protocol involving human subjects at the Cleveland Clinic while maintaining the previously approved protocol active at UCSF. Since the PI left UCSF, the name of the PI on UCSF's IRB protocol has been changed to Dr. Mack Roach, a co-investigator of this grant. For the new IRB protocol at Cleveland Clinic, the PI submitted (dated on April 13, 2010) the application of involving human research subjects to the Protocol Review and Monitoring Committee (PRMC) at the Case Cancer Center of Case Western Reserve University, where the cancer researchers of Cleveland Clinic is affiliated. After presenting the protocol in person to the PRMC and submitting two revisions, the PI obtained an approval from PRMC on May 17, 2010. The protocol then was reviewed by the full board members of The Case Cancer Center Institutional Review Board (IRB) and was approved by the IRB on July 29, 2010. The Office of Research Protections (ORP) and Human Research Protection Office (HRPO) at the United States Army Medical Research and Materiel Command (USAMRMC) approved the protocol on September 14, 2010.

(b) Pattern of the prostate movement

Among sixteen consented patients from UCSF, we were able to retrieve twenty-six useful daily MV-CBCT images from archived data of eight patients. Using these data, we analyzed the pattern of the prostate movement as stated task 1-3 in the statement of work (SOW). After double imaging registration of twenty-six daily MV-CBCTs, Figure 1 showed the pattern of the prostate movement for these patients.

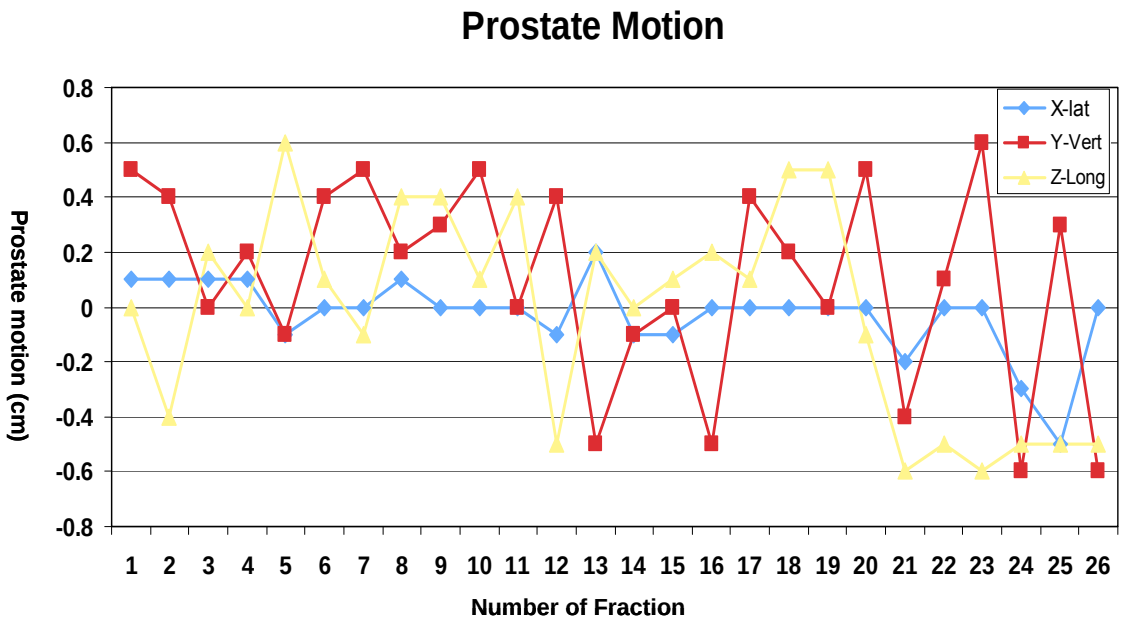

Figure 1. Prostate movement pattern obtained from dual imaging registration of MV-CBCT from 26 fractions

From this preliminary data, we confirmed the pattern of the prostate motion from this group of patients is similar to the published result but the magnitude of the prostate motion is smaller than published result, about 0.6 cm along the anterior-posterior and cranial-caudal directions. In this task, twenty-six available MV-CBCTs are not adequate for us to draw firm conclusions on the pattern of the prostate movement. We are planning to use more KV-CBCT data from Cleveland Clinic to finish this task. Nevertheless, based on this preliminary data, we designed and conducted task 2-3 in SOW, described in section (c) below. The abstract of this study was accepted and orally presented in 2010 annual meeting of American Association of Physicists in Medicine (AAPM) in Philadelphia (Appendix A). Another abstract with more enhance data has been accepted as a poster presentation in the second Innovative Minds in Prostate Cancer Today (IMPaCT) conference, sponsored by prostate cancer research program of USAMRMC (Appendix B)

(c) Practical considerations for the novel multiple adaptive planning strategy

Based on the preliminary data from Figure 1, we recognized that prostate movements can be in both direc tions s imultaneously. Failure to accommodate m ultiple direc tional m ovements may result in inadequate dose coverage for the pr ostate as we showed in the published paper [1] (appendix D). The qu estion is ho w m any pla ns can adeq uately acco unt f or m ulti-directional movements of the prostate (task 2-3 in SOW). In this study, we provided a guideline for the minimum number of plans required for clinically implementing the MAP technique.

Since the prostate often moves in the anterior/posterior and superior/inferior directions with considerable distances, for each patient, nine MAP plans are considered to accommodate prostate movements of 0.5 cm in one or two of these directions. Without requiring any additional

hardware or software, the MAP strategy is to choose a plan from the pool that most closely matches to the "prostate position of the day". This prostate position can be determined by dual image registrations: one aligned to the implant markers in the prostate and the other aligned to the pelvic bones. To validate effectiveness of this strategy, from treatment data of six patients, seventeen daily megavoltage cone beam CTs (MV-CBCT) that demonstrated large prostate movements of 0.4 cm to 0.8 cm were selected for this study. For each patient, based on the detected prostate movements, one of 9 MAP plans was retrospectively selected for treatment. The selected MAP plan was then applied to the corresponding MV-CBCT to calculate the dose delivery. Based on these MV-CBCTs, iso-center shifting plans and retrospective real-time plans were also created for these treatment days. Using these real-time plans as the benchmark, the recalculated MAP plans and the conventional iso-center shifting plans were compared in terms of dosimetric values of the prostate, pelvic lymph nodes, bladder, and rectum.

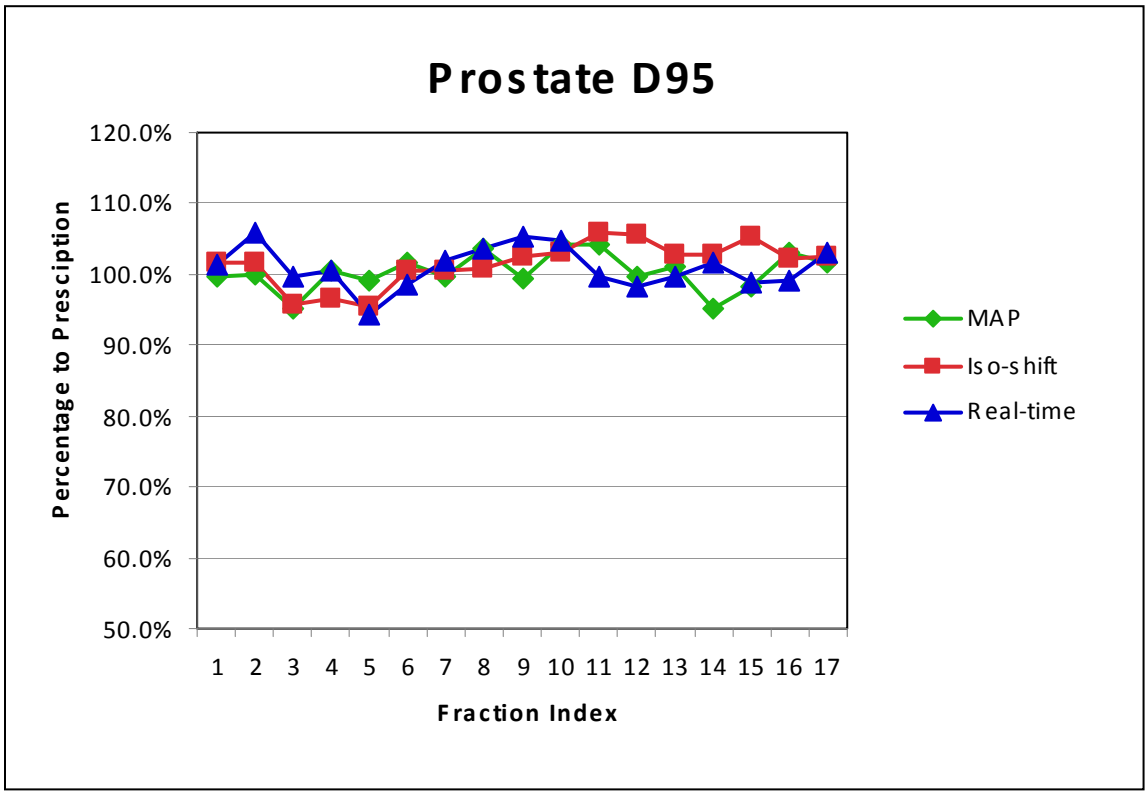

Figure 2. Comparison of MAP, Iso-shift, and real-time plans for prostate dose coverage, measured by dose to 95% of the prostate volume.

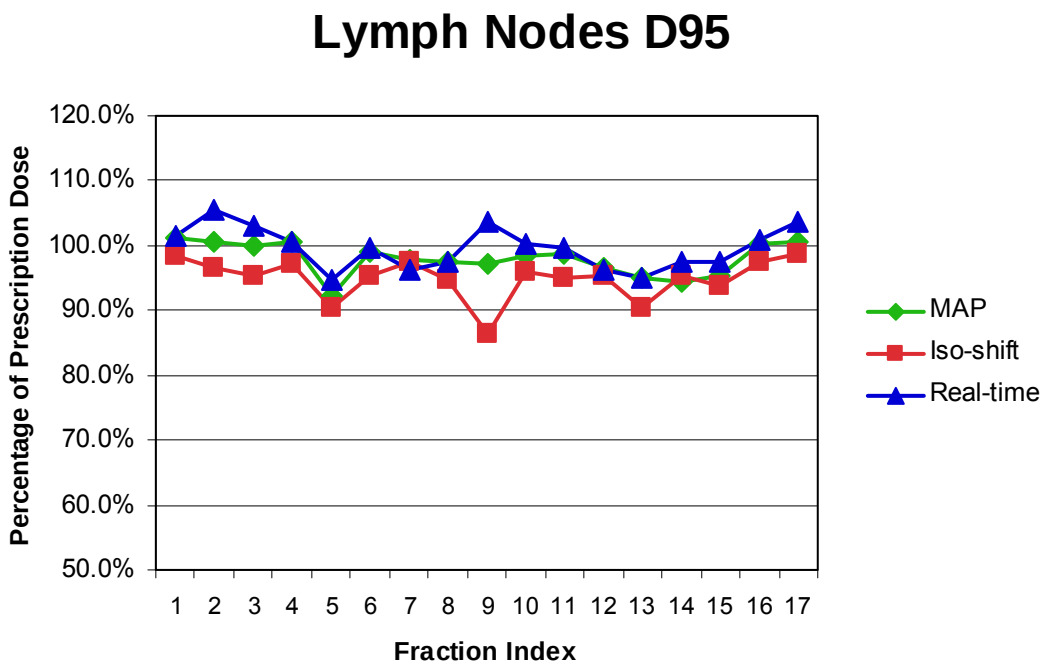

Figure 3. Comparison of MAP, Iso-shift, and real-time plans for pelvic lymph nodal volume coverage, measured by dose to 95% of the volume.

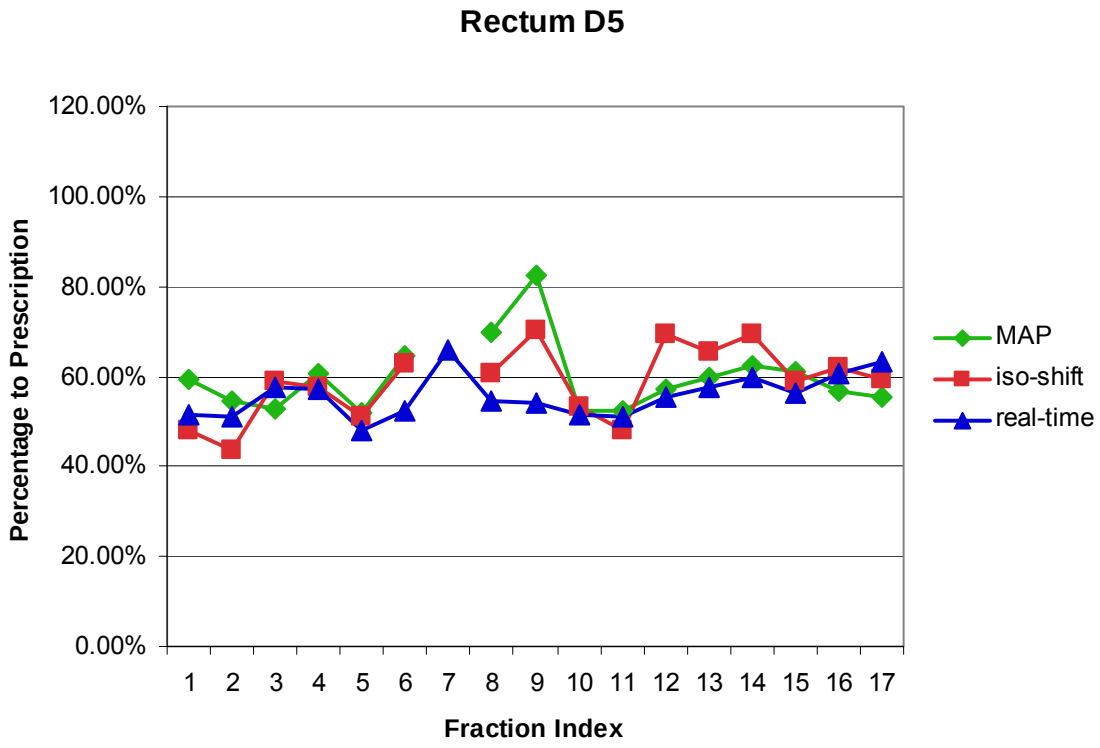

Figure 4. Comparison of MAP, Iso-shift, and real-time plans for the rectum dose, measured by maximum dose received by 5% of the volume.

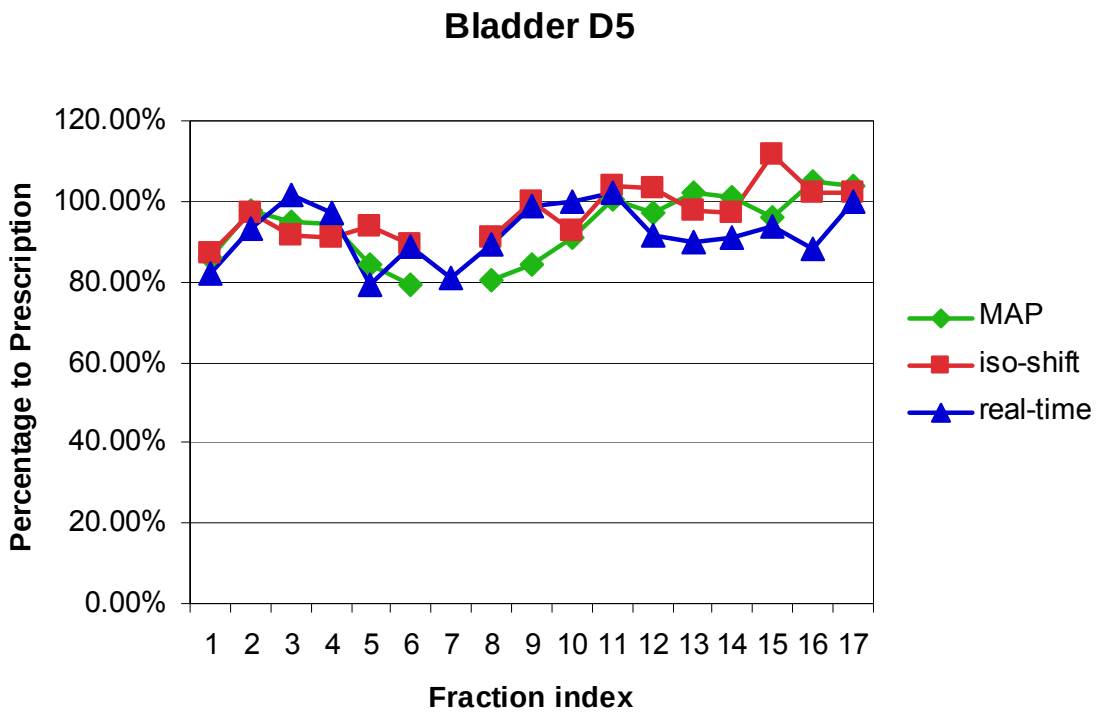

Figure 5. Comparison of MAP, Iso-shift, and real-time plans for the bladder, measured by maximum dose received by 5% of the volume.

In summary, of these fractions, the MAP, iso-center shifting, and real-time planning techniques resulted in similar dose coverage to the prostate. Correspondingly, 95% of the prostate volume would receive a daily dose > 97% of the prescription dose in 15, 16, and 16 fractions, as shown in Figure 2. The above techniques would result in 95% of the pelvic lymph node volume receiving a daily dose > 97% of the prescription dose in 12, 6, and 13 fractions, respectively (as shown in Figure 3). As shown in Figures 4 and 5, the average doses to 5% and 50% of the bladder (D5, D50), relative to the planned endpoint doses, would be 93.7% (62.0%), 97.1% (63.2%), and 92.2% (62.9%), respectively. The average D5 (D50) of the rectum relative to the planned endpoint doses would be 92.9% (59.6%), 92.5% (58.7%), and 89.8% (55.8%), respectively.

In conclusion, the use of the MAP technique with 9 pre-created plans, which accommodate for multiple independent prostate shifts, can achieve similar treatment goals as real time planning method for the treatment of high-risk prostate cancer.

(d) Computer-assisted, atlas-based segmentation

As stated in task 1-5, we were intended to develop model based contouring models to facilitate efficient delineation of the bladder and rectum for each MV-CBCT. This idea prompted us to assess whether computer-assisted segmentation can improve the consistency and efficiency of this task for prostate cancer patients treated with whole pelvic IMRT. We used a commercial program (MIM-vista, Cleveland, OH) to create both physician-specific and master atlases comprised of clinically node-negative prostate cancer patients with previously contoured volumes. Three regions of interest (ROIs) were chosen for analysis: prostate, lymph nodes, and

rectum. An independent set of patients with previously contoured ROIs was chosen to evaluate these atlases. Atlas-assisted contours were compared to manual contours by calculating a volumetric overlap index.

For the fifteen patients chosen for evaluation, the average overlap between the manually drawn and master atlas-based contours for the prostate, lymph nodes, and rectum was 60%, 51%, and 64%, respectively. There was a significant difference in the volumes of the rectum and lymph nodes (but not the prostate) for the master atlas ($p = 0.049$ and $p = 0.016$, respectively). When compared to physician-specific atlases, the average overlap between contours for these ROIs was 56%, 60%, and 60%, respectively. There was no difference in distributions between manually drawn and physician-specific atlas-assisted contours for these structures.

We found that Atlas-based segmentation for ROI delineation can potentially improve both consistency and efficiency in contouring. Regardless of whether a physician-specific atlas or a larger, more heterogeneous atlas, reasonable overlap between segmented and manually drawn ROIs was achieved.

The completed manuscript is in appendix C.

(e) Task 3 (item 1, 2 and 3) - automatically identify MLC leaf pairs

We finished the initial program design on a standard-alone personal computer, which can communicate with the treatment planning system (Pinnacle). The major functions of current program are to: (1) import original treatment plan including MLC shapes from the Pinnacle planning system, (2) automatically generate a MLC-shifted plan based on information of daily prostate shifts, and (3) export the MLC-shifted plan back to the Pinnacle planning system. As well, a complementary graphic user interface (GUI) was designed to facilitate a visual inspection of functionality of the program (shown in Figure 6). With this GUI design, contours of the prostate and pelvic lymph nodes, as well as the original and shifted MLC shapes in the beam-eye-view can be displayed. This program will improve our workflow and efficiency to finish Task 3-(item 4, 5, and 6) in next year.

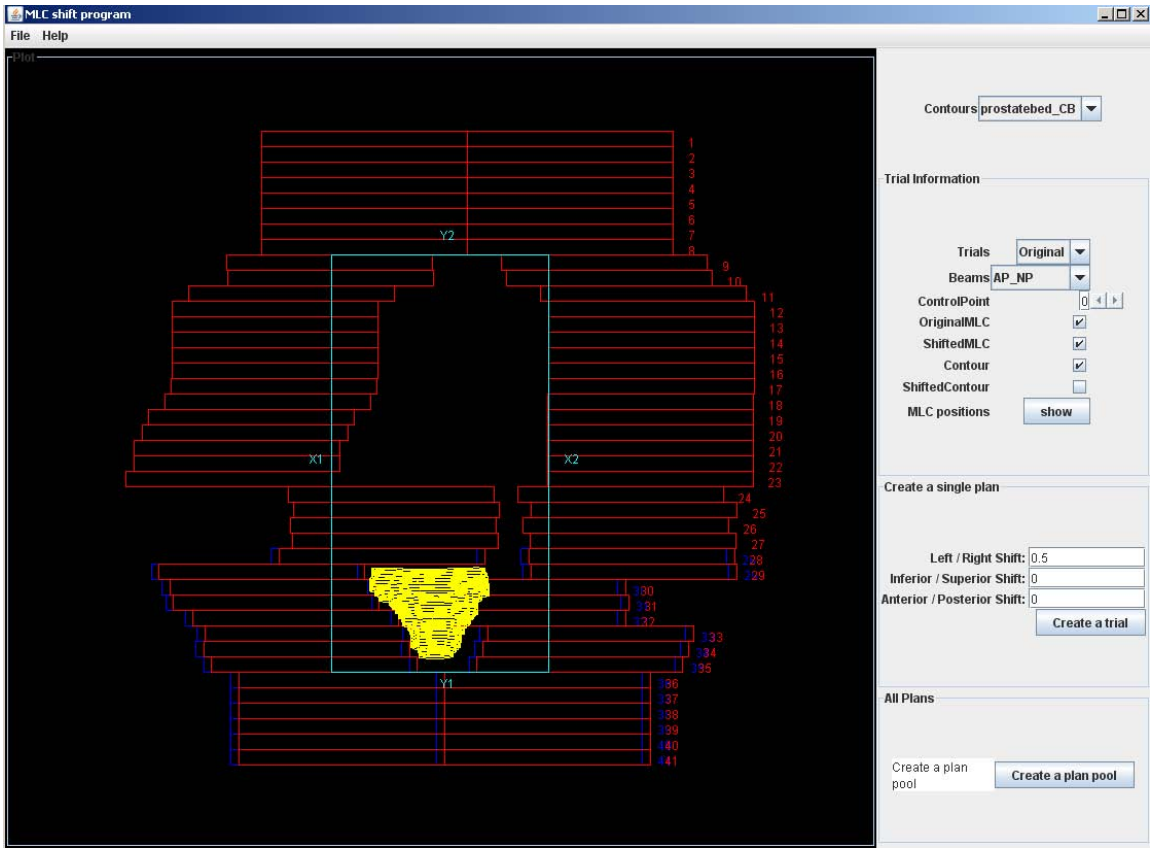

Figure 6: A snapshot of the auto-MLC shifting program.

(f) Transfer the contours of the prostate and pelvic lymph nodes

In this task (task 1-4&5), we have encountered a problem. By aligning the implanted markers inside of the prostate gland for eight patients from UCSF, large rotations were detected. These large rotations, if corrected, would result in significant body rotation and hence make patients in difficult and unstable positions. Since the soft tissue contrast is limited in MV-CBCT, it is difficult to investigate whether the detected rotations are due to the migration of the implanted markers or due to the true rotation of the prostate organ. With KV-CBCT, for patients who will be recruited from Cleveland Clinic, we believe that soft tissue contrast is adequate to deline ate the prostate gland. There is an existing protocol from Cleveland Clinic for a small number of patients, who received implanted markers as well as daily KV-CBCT. We plan to use this group of patients to investigate the encountered problem.

Key Research Accomplishments

- **(a)** We obtained IRB approval for conducting the proposed research at Cleveland Clinic while maintaining the UCSF protocol.
- **(b)** Completed task 2 (item 3) in SOW.
- **(c)** Assess whether computer-assisted, atlas-based segmentation for target volume delineation in whole pelvic IMRT for prostate cancer can improve consistency and efficiency.
- **(d)** Completed task 3 (item 1,2 and 3) in SOW.

Reportable Outcomes

(a) An abstract entitled as: "Practical considerations for the novel multiple adaptive planning strategy for patients concurrently treated with the prostate and pelvic lymph nodes ", Accepted by 2010 AAPM annual meeting. (Appendix A).

(b) An abstract entitled as: "Multi-Adaptive Plan (MAP) IMRT to Accommodate Independent Movement of the Prostate and Pelvic Lymph Nodes" Accepted by the second Innovative Minds in Prostate Cancer Today (IMPaCT) conference, sponsored by prostate cancer research program of USAMRMC (Appendix B).

(c) A manuscript entitled as: "Computer-Assisted, Atlas-Based Segmentation for Target Volume Delineation in Whole Pelvic IMRT for Prostate Cancer", will be submitted to Radiother Oncol**.** (Appendix C).

(d) An article entitled as: "Comparison of Three Strategies in Management of Independent Movement of the Prostate and Pelvic Lymph Nodes", **Med. Phys**. 37(7), 5006-5013 (2010) (Appendix D).

Conclusion

In summary, in this period of research, we successfully obtained another IRB approval for the study while maintaining the UCSF IRB active. We found that the bi-directional prostate shifts, particular in anterior-posterior and superior-inferior directions, must be considered with the multiple adaptive plan (MAP) strategy. With this strategy, the verification plans calculated with daily MV-CBCT can achieve a similar dose coverage for the prostate and pelvic lymph nodes while adequate protecting the rectum and bladder. Furthermore, computer-assisted, atlas based segmentation can improve consistency and efficiency in delineating volumes of the prostate and pelvic lymph nodes. Our future study will investigate whether the MLC-shifting strategy can effectively produce multiple plans for the multiple adaptive plan strategy and improve clinical work efficiency.

References

(1) Xia P, Qi P, Hwang A, Kinsey E, Pouliot J, Roach III M: "Comparison of Three Strategies in Management of Independent Movement of the Prostate and Pelvic Lymph Nodes**",** *Med Phys.* 2010 Sept;37(9):5006-13. (2010)

Appendices

Appendix A

Abstract:

Practical considerations for the novel multiple adaptive planning strategy for patients concurrently treated with the prostate and pelvic lymph nodes

Peng Qi, Jean Pouliot, Mack Roach III, and Ping Xia

Accepted as an oral presentation in the annul meeting of American Association of physicists in Medicine (AAPM) of 2010.

Purpose: Our previous work presented the feasibility of a novel adaptive strategy, multiple adaptive planning (MAP), for the concurrent treatment of the prostate and lymph nodes. The question raised for this technique is how many plans can adequately account for multi-directional movements of the prostate. In this study, we provide a guideline for the minimum number of plans required for clinically implementing the MAP technique.

Methods and Materials: Data from five patients with high-risk prostate cancer, who have undergone IMRT, were selected for this study. Without including lateral prostate shifts, combinations of anterior/posterior and superior/inferior shifts of 0 cm and 0.5 cm were considered. Correspondingly, a total of 9 IMRT plans were prepared for the following treatment. Double Image registrations between daily MVCBCT and the planning CT were conducted to identify independent prostate shifts. Based on this information, a most suitable plan was retrospectively selected and recalculated using the daily CBCT images. For comparison, the corresponding iso-center shifting plans were also created.

Results: For 20 fractions from 5 patients, prostate shifts in the range between 0.4 cm and 0.8 cm, were observed in 13 fractions. Of these fractions, conventional iso-tracking method would result in adequate dose coverage of the lymph nodes in only 37% days compared to 100% days in MAP strategy. Both strategies achieved 95% of the prostate receiving a daily dose > 97% of the prescription dose in 11, 12 fractions, respectively. Furthermore, the average D50 of the rectum and bladder in the iso-tracking plans, 29.9 Gy and 31.5 Gy, were higher than those, 28.9 Gy and 28.9 Gy, in the MAP plans.

Conclusion: Using of the MAP technique with 9 pre-created plans, which accommodate for independent prostate shifts, can achieve our treatment goals for the treatment of high-risk prostate cancer.

Research partly sponsored by the USAMRMC (PC073349).

Appendix B:

Abstract: Multi-Adaptive Plan (MAP) IMRT to Accommodate Independent Movement of the Prostate and Pelvic Lymph Nodes

Ping Xia, Peng Qi, Jean Pouliot, Mack Roach III

Accepted as a poster presentation in the second Innovative Minds in Prostate Cancer Today (IMPaCT) conference, sponsored by prostate cancer research program of USAMRMC.

Purpose: Concurrent irradiation of the prostate and pelvic lymph nodes is technically challenging due to treating one moving target and one immobile target. Real time planning would be an ideal method, but this method is not clinically feasible due to many technical and logistical challenges. The purposes of this project are to propose a new management strategy and to compare this strategy with the conventional isocenter shifting method using retrospectively created real time plans as a benchmark.

Methods/Materials: The proposed new management strategy, referred to as Multiple Adaptive Plans (MAP), creates a pool of plans for several most likely prostate locations. Since the prostate often moves in the anterior/posterior and superior/inferior directions, for each patient, nine MAP plans are considered to accommodate prostate movements of 0.5 cm in one or two of these directions. Without requiring any additional hardware or software, the MAP strategy is to choose a plan from the pool that most closely matches to the "prostate position of the day". This prostate position can be determined by dual image registrations: one aligned to the implant markers in the prostate and the other aligned to the pelvic bones. To validate effectiveness of this strategy, from treatment data of six patients, seventeen daily megavoltage cone beam CTs (MV-CBCT) that demonstrated large prostate movements of 0.4 cm to 0.8 cm were selected for this study. For each patient, based on the detected prostate movements, one of 9 MAP plans was retrospectively selected for treatment. The selected MAP plan was then applied to the corresponding MV-CBCT to calculate the delivery. Based on these MV-CBCTs, is-center shifting plans and retrospective real time plans were also created for these treatment days. Using these real time plans as the benchmark, the recalculated MAP plans and the conventional isocenter shifting plans were compared in terms of dosimetric values of the prostate, pelvic lymph nodes, bladder, and rectum.

Results: Of these fractions, the MAP, iso-center shifting, and real-time planning techniques resulted in similar dose coverage to the prostate. Correspondingly, 95% of the prostate volume would receive a daily dose > 97% of the prescription dose in 15, 16, 16 fractions. The above techniques would result in 95% of the pelvic lymph node volume receiving a daily dose > 97% of the prescription dose in 12, 6, 13 fractions, respectively. The average doses to 5% and 50% of the bladder (D5, D50), relative to the planned endpoint doses, would be 93.7% (62.0%), 97.1% (63.2%), and 92.2% (62.9%), respectively. The average D5 (D50) of the rectum relative to the planned endpoint doses would be 92.9% (59.6%), 92.5% (58.7%), and 89.8% (55.8%), respectively.

Conclusion: Using of the MAP technique with 9 pre-created plans, which accommodate for independent prostate shifts, can achieve our treatment goals for the treatment of high-risk prostate cancer.

Impact: The proposed MAP strategy can be directly applied into clinical practice immediately although it may require extra effort in treatment planning. Our future research will seek a solution to minimize this planning effort.

Appendix C

Computer-Assisted, Atlas-Based Segmentation for Target Volume Delineation in Whole Pelvic IMRT for Prostate Cancer

Sunanda Pejavar, M.D., Andrew Hwang, Ph.D., Joycelyn Speight, M.D., Ph.D., Alexander Gottschalk, M.D., Ph.D., I-Chow Hsu, M.D., Sue Sun Yom, M.D., Ph.D., Mack Roach III, M.D., F.A.C.R., Ping Xia, Ph.D.

ABSTRACT

Purpose: Target volume delineation has become a laborious task in the era of IMRT, and large variations have been observed. This project evaluated whether computer-assisted segmentation can improve the consistency and efficiency of this task for prostate cancer patients treated with whole pelvic IMRT. Materials and Methods: A commercial program was utilized to create both physician-specific and master atlases comprised of clinically node-negative prostate cancer patients with previously contoured volumes. Three regions of interest (ROIs) were chosen for analysis: prostate, lymph nodes, and rectum. An independent set of patients with previously contoured ROIs was chosen to evaluate these atlases. Atlas-assisted contours were compared to manual contours by calculating a volumetric overlap index. Results: For the fifteen patients chosen for evaluation, the average overlap between the manually drawn and master atlas-based contours for the prostate, lymph nodes, and rectum was 60%, 51%, and 64%, respectively. There was a significant difference in the volumes of the rectum and lymph nodes (but not the prostate) for the master atlas ($p = 0.049$ and $p = 0.016$, respectively). When compared to physician-specific atlases, the average overlap between contours for these ROIs was 56%, 60%, and 60%, respectively. There was no difference in distributions between manually drawn and physician-specific atlas-assisted contours for these structures. Conclusions: Atlas-based segmentation for ROI delineation can potentially improve both consistency and efficiency in contouring. Regardless of whether a physician-specific atlas or a larger, more heterogeneous atlas, reasonable overlap between segmented and manually drawn ROIs was achieved.

Acknowledgment:

This research is supported in part by the United States Army Medical Research and Materiel Command (USAMRMC, PC073349).

Advances in radiotherapy have made intensity-modulated radiation therapy (IMRT) an effective and widely used modality in the treatment of various malignancies. In particular, IMRT has become standard practice in the treatment of localized prostate cancer. The dosimetric superiority of IMRT over conventional external beam techniques has allowed for better conformality to target volumes and improved sparing of critical normal tissues. Enhanced dose distributions have made it possible to dose escalate, resulting in both improved tumor control and reduced treatment toxicity.

Conformal radiotherapy techniques such as IMRT are based on accurate delineation of target volumes using computed tomography (CT) planning systems. In the case of advanced prostate cancer, whole pelvic IMRT may involve contouring the prostate, lymph nodes, and seminal vesicles as well as various regional normal structures. Physicians working in high-volume centers must allocate a significant amount of time and resources for this laborious job. Several studies [1] [2] have highlighted the time-consuming nature of manual contouring for IMRT in the treatment of both prostate and head and neck (HN) cancer. Miles et al reported an average of 1.4 hours and 2.3 hours spent on target volume delineation per patient treated for prostate and HN cancer, respectively. [1] Hong et al showed that physicians spent an average of 100 minutes contouring HN tumor volumes and critical structures. [2]

Substantial variations have also been observed amongst physicians in the contouring of target volumes and critical structures Hong et al observed significant differences in the determination (what to include) and delineation (where to contour) of HN targets amongst 20 physicians from various well-known institutions [2]. A recent study reported by Lawton et al also showed significant disagreements in the definitions of iliac and presacral clinical target

volumes (CTVs) for pelvic nodal radiation between different genitourinary radiation oncologists. [3]

There has been an increasing amount of literature recently on the use of computer-assisted target volume delineation (CAT) systems for contouring. Several studies have shown promising results in decreasing the amount of time spent on this laborious task as well as reducing variation amongst physicians contouring the same structures.[4] The purpose of this study was to evaluate whether computer-assisted segmentation using an atlas could improve both the efficiency and consistency of target volume delineation in prostate cancer patients treated with whole pelvic IMRT.

Computer-Assisted Target Volume Delineation (CAT) System

A commercially available program was used for atlas creation and subsequent segmentation (automatic contour generation). An overview of the steps involved in this process is shown in Figure 1. Assuming that pelvic lymph node distributions are not drastically different from patient to patient, those who have similar pelvic bony anatomy presumably share similar pelvic node distributions, excluding enlarged lymph nodes. Based on this assumption, an uncontoured computed tomography (CT) scan of a subject can be automatically segmented based on previously contoured CT scans of patients who have similar pelvic anatomy. A library (or "atlas") can be constructed, that is composed of selected CT scans with previously contoured target volumes and critical structures, and used for computer assisted target volume delineation (CAT). In the CAT system used for this study (MIM-vista, Cleveland, OH), the best matching atlas patient is chosen automatically based on user defined selection criteria, and then deformable image registration is carried out between the two CT scans to correct for anatomical differences. Contours are then deformably transformed from the atlas patient to the subject patient's CT scan. The automated portion of the procedure by the CAT system takes approximately one to two minutes.

Atlas Construction

Our atlases consisted of clinically node-negative patients with intermediate to high risk prostate cancer treated with whole pelvic IMRT by one of four board-certified radiation oncologists at our institution specializing in prostate cancer. All four physicians have annual prostate IMRT experience of 30 cases or more, and have been practicing radiation oncology for an average of 11 years (range 8 to 19 years) at our institution. The regions of interest (ROIs) had been previously

contoured on these patients' planning CT scans by the treating physician, and included the prostate, seminal vesicles, lymph nodes, bladder, and rectum. Contouring on all patients was done on the Pinnacle treatment planning system (Philips Medical Center, Bothell, WA). For this study, several atlases were constructed. Four separate physician-specific atlases were constructed, each comprised of only the patients treated by that particular physician. A master atlas comprised of all the patients was also created.

Segmentation

A second, independent set of patients was chosen for segmentation by the CAT system and designated as "subjects". These patients were also clinically node-negative patients with intermediate to high risk prostate cancer who had been treated with whole pelvic IMRT by the same four radiation oncologists. Although these patients also had previously contoured ROIs, their blank planning CT scans were used for segmentation; the manual contours were used for analysis only. Segmentation was performed on each of the subjects twice, once using the corresponding physician-specific atlas and once using the master atlas. Therefore, two sets of automatically generated segmented contours were generated for each subject.

Analysis

Three ROIs were chosen for analysis: prostate, lymph nodes, and rectum. Segmented contours were compared to manually drawn contours by calculating volume overlap and volume difference between the two contours. These calculations were carried out for each ROI and for contours generated by both the master and attending atlases. The equations used for these calculations are shown in Figure 2. The paired t-test was used to test the significance of differences in volumetric overlap and volume difference between the attending and master

atlases for each ROI, as well as between the manually drawn contours and the atlas-based contours (master and physician-specific) for each ROI.

Radiation Therapy Oncology Group (RTOG) Guidelines

In 2007, a consensus meeting was held by the RTOG to reach agreement on CT image- based pelvic lymph node volumes in the treatment of genitourinary cancers with whole pelvic IMRT. Based on this consensus, the volumes to be irradiated include: distal common iliac, presacral lymph nodes (S1-S3), external iliac lymph nodes, internal iliac lymph nodes, and obturator lymph nodes. Lymph node CTVs include the vessels (artery and vein) and a 7-mm radial margin being careful to avoid, or "carve out", bowel, bladder, bone, and muscle. Volumes begin superiorly at the L5/S1 interspace and end at the superior aspect of the pubic bone. The manually contoured lymph node volumes from this study were compared to the current RTOG consensus guidelines in order to evaluate discrepancies. Current RTOG consensus guidelines and a representative axial slice showing nodal contours are summarized in Figure 3.

Atlas Characteristics

Table 1 shows characteristics of the master and physician-specific atlases. The master atlas contained a total of 44 patients, and each of the four physician specific atlases contained between 9 and 13 patients. All but one patient had a histology of adenocarcinoma, and all were clinically node-negative (cN0). The majority of patients (50%) were Gleason grade 7. Most patients had stage T2 cancer, although there was a fairly even distribution between various stages. A little over half the patients (55%) had PSA values of 10 or less. Weight and bladder volume were recorded.

Subject Characteristics

There were a total of 15 subjects, treated by three of the four physicians. The final physician had an insufficient number of prostate patients treated with IMRT for inclusion in the atlas as subjects. Table 2 summarizes the characteristics of the subject patients.

Volume overlap

A side-by-side comparison of a patient with manually drawn contours and segmented contours is shown in Figure 4. Note that the contours segmented from the CAT system more closely mimic the RTOG consensus guidelines. Axial, coronal, and sagittal images of a patient segmented by a physician-specific atlas and the master atlas are shown in Figure 5. Note the differences in nodal volumes and borders.

Volume overlap and volume difference were calculated. When segmented from the master atlas, the average overlap between the manually drawn and atlas-based contours for the prostate, lymph nodes, and rectum was 60%, 51%, and 64%, respectively. The average volume

difference for these ROIs was 34%, 29%, and 27%, respectively. When segmented from the physician-specific atlases, the average overlap between contours for these ROIs was 56%, 60%, and 60%, respectively. The average volume difference for these ROIs was 38%, 20%, and 33%. A summary is shown in Table 3. When contours segmented by the master atlas were compared to those segmented by the physician-specific atlas, differences in both volume overlap and volume difference were significant for nodal contours ($p = 0.02$). Volume overlap and volume difference between the master and physician-specific atlases for prostate and rectum contours were not significant. When manually drawn contours were compared to master atlas-based contours, there was a statistically significant difference in the volumes of the rectum and lymph nodes ($p = 0.049$ and $p = 0.016$, respectively), but not the prostate. There was no difference between the distributions between the manually drawn contours and contours segmented from physician-specific atlases for any of the three structures (Table 3).

Time-saving

Atlas-based segmentation took approximately two minutes per patient, compared to an estimated manual contouring time of 1.5 hours.

In summary, atlas-based segmentation (ABS) for ROI delineation in whole pelvic IMRT using our CAT system was shown to potentially improve both efficiency and consistency in the contouring process. These findings have important implications in clinical radiation oncology practice because of the rapidly growing acceptance and use of IMRT. Mell et al reported the results of a survey conducted amongst 500 radiation oncologists on their use of IMRT. [5, 6] Between 2002 and 2004, the use of IMRT increased overall from 32% to 67.8%, and the most common site treated with IMRT by 2004 was genitourinary (84.5%). Amongst physicians using IMRT in 2004, the vast majority stated that they planned on increasing (62.8%) or maintaining (35.8%) their use in the coming years. Moreover, of the physicians not currently using IMRT, over 90% stated that they would implement IMRT in the future, with 59.4% planning to adopt it within the next year.

The widespread use of IMRT in the treatment of prostate cancer has resulted in increased clinical workload and allocation of additional resources due to the complexity of IMRT compared with conventional techniques. In the report by Miles et al, IMRT was found to increase overall planning times and in particular, impact clinician and physicist workflow. The major bottleneck for clinicians involves contouring time, and in this study that task averaged 2.3 hours in head and neck IMRT (range 0.7 to 3.5 h) and 1.4 hours (range 0.9 to 2.2 h) in prostate and pelvic node IMRT. [1] Hong et al also measured the time required by physicians to contour HN targets and found that physicians spent an average of 1 hour and 40 minutes (range 60 to 210 minutes) on this contouring. [2] Other studies reported times of between 3 and 10 hours for whole pelvic IMRT planning [7, 8], although little information was available regarding the times spent on individual stages of the planning process.

Variability in target volume delineation has also become an increasing concern for studying and comparing treatment outcomes in the era of IMRT. Possible reasons for the inconsistencies between physicians include differences in training and experience, discrepancies in the understanding of microscopic extension of disease and patterns of nodal spread, and variable interpretation of anatomical differences on CT scans. Several reports have been published showing variability in the determination and delineation of target volumes for several different tumor sites, including bladder, breast, HN, and prostate. A recent report by Li et al showed substantial variability in breast cancer target volumes and normal structure contours between multiple institutions and observers, with structure overlap as low as 10% and volume variations with standard deviations of up to 60%. [9] In a study by Fiorino et al, significant inter-observer variability was shown amongst five radiation oncologists contouring the prostate and seminal vesicles of patients previously treated with conformal techniques [10]. Similarly, Cazzaniga et al showed variability in the manual delineation of the PTV in three different prostate cancer patients, both in the cranio-caudal direction and extension of tumor on separate axial CT slices [11].

Maintaining consistency in the contouring of lymph nodes is particularly important in whole pelvic IMRT. Several studies have shown that pelvic nodal irradiation may directly impact outcome in high risk prostate cancer patients who have a significant risk of nodal involvement.[12-14]. Treatment of pelvic nodes is now considered a standard in these patients and is also required in two current Radiation Therapy Oncology Group (RTOG) trials (05-21 and 05-34). A consensus guideline for the delineation of lymph node volumes for whole pelvic IMRT does exist. [15]; however, these guidelines are frequently subject to modification or revision. Moreover, despite the presence of consensus guidelines, variability in the delineation of these volumes exists. In a comparative study of clinical target volume (CTV) definition of pelvic lymph nodes by Lawton et al, significant variation in the delineation of iliac and presacral

CTVs was seen amongst multiple radiation oncologists. [3] As indicated in our study, a large number of manual nodal contours differed from each other as well as from the RTOG consensus guidelines. The fact that there was a significant difference in the volume overlap and volume difference between the master and physician-specific atlases, as well as between manually drawn nodal contours and nodal contours segmented from the master atlas, suggests that this variability exists within our institution as well. By generating contours from a large master atlas, it seems feasible that these inconsistencies could be reduced. There has been recent interest in the use of new imaging techniques such as MR lymphography for lymph node topography in order to develop an accurate, objective description of the nodal locations for radiation treatment planning. [16] [17] With these newer techniques, it will likely become even more important to define and implement consistency in the contouring of pelvic lymph nodes.

Several different groups have evaluated the applicability and feasibility of semiautomatic CAT systems for target volume delineation. Reed et al described a deformable image registration-based breast segmentation method to generate a clinical target volume from a template case with a consensus contour definition to a new patient. [18] This method improved both consistency and efficiency compared with manual contouring. Another study by Lu et al looked at a recontouring method based on deformable image registration that was validated in the setting of four-dimensional CT planning for lung cancer. [19] Chao et al developed a deformable image registration using a CAT system that mapped HN contours from a template case to a patient with similar clinical characteristics. [4] Eight radiation oncologists performed target delineation on two cases, one with a base of tongue cancer and one with a nasopharyx cancer (NPC), first by contouring regions of interest from scratch and then by editing deformed contours. Geometric and volumetric variations as well as time spent on contouring and editing were evaluated. The study found that there was significant variability between the manual contours drawn by different physicians and that this variability was reduced by generating

contours using the deformable image registration. Average timesaving was 26% to 29% for more experienced physicians and 38% to 47% for less experienced physicians.

Two recent studies have highlighted the timesavings of atlas-based segmentation in particular for contour generation. In the study by Chao et al, timesavings was evaluated both by site and physician experience ("less experienced" physicians were those with 20 IMRT cases or less annually). Average timesavings for base of tongue (BOT) cancer and nasopharynx cancer (NPC) were 26 and 29%, respectively, amongst experienced physicians and 47% and 38%, respectively, for less experienced physicians. [4] In another abstract reported by Hu et al, the same commercially available software that was used in this study was employed for atlas creation and segmentation of head and neck IMRT patients. Patients treated at two different institutions were randomly chosen, and the times required for ABS and manual contouring by an attending physician were recorded. At institution 1, ABS proved to be almost as helpful to the attending physician as resident contours, and resulted in an overall timesavings of 87% for normal structures, nodal targets, and primary targets. At institution 2, there was a 68% decrease in contouring time for nodal targets and normal structures, but only a 25% reduction in time for primary targets. The authors noted that the patients chosen at institution 2 had uncharacteristically early stage cancers and therefore required less complex contouring than those at institution 2. This finding may explain the discrepancy between the timesavings experienced at the two institutions. [20]

In another recent abstract by Lin et al [21], ABS was applied to prostate IMRT patients. There was a significant reduction in the time required to contour and edit a patient, with a 47.4% decrease in contour generation time by the resident physician and a 36% reduction in editing time by the attending physician. The most time savings was experienced in generating contours for the femurs (54.1%), followed by the prostate (46.2%) and bladder (45%), and finally the

rectum (34.9%). Unlike our study, pelvic lymph nodes were not included as an ROI in this abstract. [21]

Similar to the reports above, the present study did show that atlas-based segmentation could potentially reduce the time spent on contouring regions of interest in whole pelvic IMRT. However, the main focus of our study was not to show time savings but rather to demonstrate the feasibility of atlas-based segmentation in generating accurate and consistent contours, particularly for pelvic lymph nodes. The overlap between segmented and manual contours, or the degree of similarity between the contours generated by the CAT system and those drawn by the physician, was between 50% and 64%. One might assume that in an ideal situation this overlap would approach 100%. However, auto-segmented contours are meant to represent a good starting point for editing, not a substitute for manual contours. Consensus guidelines are constantly changed and updated, and furthermore each patient must be assessed on a case-by-case basis. Clinical judgment is still of utmost importance in treating patients and therefore editing of segmented contours is still a necessary component of these new CAT-based systems.

Although reasonable overlap was achieved between manual and segmented contours in our study, several areas of future research remain. By increasing the number of patients in an atlas and improving consensus among radiation oncologists , improvement in consistency and efficiency is expected. Additional parameters, such as bladder volume, patient weight, or pelvic inlet diameter, can also be set during segmentation to potentially fine-tune the matching process.

CONCLUSIONS

Atlas-based segmentation for ROI delineation can potentially improve both consistency and efficiency in contouring. A reasonable overlap between segmented and manually drawn ROIs was achieved, regardless of whether a physician-specific atlas or a larger, more heterogenous master atlas was used. Modifying atlas-based contours rather than drawing contours from scratch may save time and improve consistency amongst different radiation oncologists.

FIGURE LEGENDS

Figure 1: Overview of Atlas-Based Segmentation (A shows Atlas Construction; B shows Segmentation).

Figure 2: Definition of DSC (Dice similarity coefficient) = # of voxels in the intersection between A and B divided by average # of voxels in A and B.

Figure 3: RTOG Consensus Guidelines for Whole Pelvic IMRT in Prostate Cancer (2008 GU Cancers Symposium).

Figure 4: Comparison between RTOG Consensus Contours , Manual Contours, and Segmented Contours

Figure 5: Comparison of Segmentation by Physician-Specific Atlas and Master Atlas

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Appendix D

A separate PDF file.

Comparison of three strategies in management of independent movement of the prostate and pelvic lymph nodes

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Purpose: Concurrent irradiation of the prostate and pelvic lymph nodes is technically challenging due to treating one moving target and one immobile target. The purposes of this article are to propose a new management strategy and to compare this strategy to the conventional isocenter shift method and the previously proposed MLC-shifting method.
Methods: To cope with two target volumes (one moving and one immobile), the authors propose a new management strategy referred to as multiple adaptive plans (MAPs). This strategy involves the creation of a pool of plans for a number of potential prostate locations. Without requiring any additional hardware or software, the MAP strategy is to choose a plan from the pool that most closely matches the "prostate position of the day." This position can be determined by dual image registrations: One aligned to the implant markers in the prostate and the other aligned to the pelvic bones. This strategy was clinically implemented for a special patient with high risk prostate cancer and pathologically confirmed positive pelvic lymph nodes, requiring concurrent IMRT treatment of the prostate and pelvic lymph nodes. Because this patient had an abdominal kidney, small planning margins around the both targets were desired. Using 17 daily acquired megavoltage cone beam CTs (CBCTs), three sets of validation plans were calculated to retrospectively evaluate the MAP strategy as well as the isoshifting and MLC-shifting strategies.
Results: According to the validation plans, MAP, isoshifting, and MLC-shifting strategies resulted in $D95$ of the prostate $>95\%$ of the daily dose on 65%, 100%, and 100% treatment days, respectively. Similarly, $D95$ of the pelvic lymph nodal was $>95\%$ of the daily dose on 100%, 75%, and 94% of treatment days, respectively.
Conclusions: None of the above strategies simultaneously achieved all treatment goals. Among the three strategies, the MLC shifting was most successful. Validation plans based on daily CBCTs are useful to evaluate the effectiveness of the motion management strategies and to provide additional dose guidance if further dose compensation is needed. [DOI: 10.1118/1.3480505]

Key words: movement management, adaptive strategy, prostate cancer, intensity-modulated radiotherapy, and image-guided radiotherapy

I. INTRODUCTION

Although the prophylactic irradiation of lymph nodes is a routine practice for many cancer sites, the role of pelvic lymph node irradiation in the treatment of localized prostate cancer is controversial. Since the initial reports in the 1980s,[1,2] the typical four-field treatment technique for pelvic irradiation has largely remained unchanged. With this conventional technique, the benefits and risks of pelvic irradiation have been debated for more than two decades.[1,3–5] Using a novel magnetic resonance lymphangiographic technique, Shih *et al.*[6] showed that the conventional field borders, defined according to the bony anatomy, do not adequately include the pelvic lymph nodal regions, resulting in poor radiation dose coverage.[7] Despite this inadequate dose coverage, investigators from the Radiation Therapy Oncology Group (RTOG) still demonstrated progression free survival benefit with prophylactic pelvic nodal lymph irradiation.[8]

For the prostate only treatment,[9,10] intensity-modulated radiotherapy (IMRT) has shown significant clinical advantages over conventional and three-dimensional conformal radiotherapy. There is also a growing body of data[7,11] suggesting that IMRT provides even greater advantages when pelvic nodes are being irradiated. For the concurrent treatment of the prostate and pelvic lymph nodes, one[7] of our previous studies reported that IMRT plans not only significantly improved the dose coverage to the pelvic lymph nodes but also greatly reduced the doses to the rectum, bladder, and the

small bowel. However, this concurrent treatment of the prostate and the pelvic lymph nodes poses the new technical challenge of simultaneously treating a moving organ and an immobile tumor volume.

Several previous studies suggest that movement of the prostate may vary from a few millimeters up to 1.5 cm relative to the pelvic bones.[12–14] In contrast, the pelvic lymph nodes are relatively fixed in close proximity to vascular structures,[6] which are presumably fixed with respect to the pelvic bony anatomy.[15] This independent movement of two targeted volumes may require a large planning margin on one of the targets, depending on how the daily images are aligned. If the daily images are aligned to the pelvic bones, a large planning margin around the prostate would be needed. If the daily images are aligned to the prostate, a large planning margin would be needed for the pelvic lymph nodes. Both alignment methods would result in the inclusion of normal structures in the high dose area of the radiation fields, increasing the risk of normal tissue complications. Depending on the risk and benefit trade-off for a specific patient at the discretion of the treating physician, either alignment method could be clinically reasonable. The challenge is to satisfy the demand of achieving dose coverage while using a small planning margin for both targets.

The ideal approach to resolve this challenge is real time replanning on a daily basis, but because of extended planning time, real time replanning is not currently practical. Without requiring real time dose recalculation, we have proposed a MLC leaf-shifting algorithm to provide an alternative solution.[16] The clinical implementation of this MLC-shifting approach requires a new feature in the record and verify system, which would allow users to adjust the MLC leaf positions at the treatment console in near real time. To circumvent this obstacle, in this paper, we proposed another strategy of creating a pool of IMRT plans to accommodate multiple presumed prostate positions. This strategy is referred to as multiple adaptive plan (MAP) IMRT. This strategy was implemented clinically for a special patient, for whom small planning margins around the prostate and the pelvic lymph nodes were demanded. Using the daily volumetric imaging acquired for the patient, we retrospectively evaluated and compared three strategies in the management of independent movement of the prostate and pelvic lymph nodes including MAP, isoshifting, and MLC-shifting strategies. In this paper, the isoshifting strategy consists of shifting the treatment isocenter based on the prostate movement relative to the pelvic bones. Because the pattern of prostate motion varies from patient to patient, the result of this comparison may not be directly generalized to other patients. The purpose of this paper is to explore the feasibility and limitations of each strategy.

II. MATERIALS AND METHODS

II.A. Multiple adaptive plan strategy

With the MAP strategy, a pool of IMRT plans was created based on a planning CT and each plan was individually optimized to accommodate a presumed prostate position. Because the number of possible prostate positions for each patient could be very large, for a special case (described below), we created a pool of five plans to compensate for prostate movements of 0.5 and 1.0 cm in the posterior and superior directions. To keep the number of plans in the pool and the workload reasonable, the prostate movement in the inferior and anterior directions was compensated by adding a 0.6 cm margin. It was assumed that lateral motion of the prostate is negligible[12–14] and the enlarged inferior and anterior margins had a minimum impact on rectal sparing.[17] An additional 0.2 cm planning margin in the posterior, superior, and lateral directions for the prostate accounted for uncertainties such as image registration uncertainty. The planning margin for the pelvic lymph nodes was 0.5 cm.

During treatment planning, five shifted prostate contours in the superior and posterior directions were created using an in-house program that read in the coordinates of the original prostate contours and shifted the coordinates of the contour to the presumed positions. These shifted prostate contours were input back into the treatment planning system (Pinnacle, version 7.6, Philips Medical Systems, Andover, MA) and appended in the set of planning contours for the patient. The initial IMRT plan for the patient was created based on our established planning protocol published elsewhere.[7,18] Briefly, most patients were first treated with 54 Gy (2 Gy/fraction) to the prostate and seminal vesicles, with concurrent pelvic lymph node dose of 48.6 Gy (1.8 Gy/fraction). The prostate and seminal vesicles then received an additional cone-down dose of 18 Gy (2 Gy/fraction), bringing the total dose to 72 Gy. All of these doses were prescribed to cover 95% of the planning tumor volume (PTV). 18 MV photons were used throughout the treatment. All IMRT plans were delivered with a step and shoot method using Siemens Linear Accelerators (Oncor, Siemens Medical Solution, Concord, CA). The first portion of the treatment used 45 segments and seven beam angles (0°, 35°, 90°, 160°, 200°, 270°, and 315° in IEC convention). The second cone-down portion of the treatment used 25 segments and seven slightly different beam angles (0°, 55°, 90°, 135°, 225°, 270°, and 305° in IEC convention). A planning dose constraint template has been published elsewhere.[18]

For the MAP strategy, all plans were created with shifted prostate contours except for the initial plan, which was based on the anatomy of the planning CT. Since the rectum and bladder were not shifted with the prostate, the anatomic relationship of these two organs with the shifted prostate was invalidated, rendering the initial planning dose constraints to the rectum and bladder irrelevant. To circumvent this problem, we constructed an artificial rind structure[19] around the shifted prostate to guide the planning system to produce highly conformal plans, thus effectively protecting the rectum and bladder. Figure 1 shows isodose distributions for five prostate positions, demonstrating that similarly conformal dose distributions can be achieved with this planning tactic.

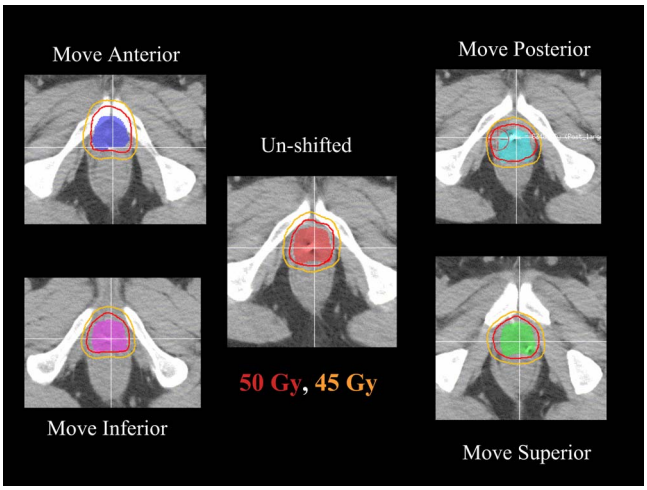

FIG. 1. Dose distributions of five MAP-IMRT plans displayed axial images, demonstrating similar conformal distributions in shifted plans can be achieved as the unshifted plan when using a rind structure.

II.B. Isoshifting strategy

For prostate only treatment, shifting the treatment isocenter based on implanted markers inside the prostate is an effective strategy, which has been routinely used clinically. It should be noted that the isocenter shifts determined with this procedure often include two components: Prostate motion relative to the bony structure and patient setup error. For prostate only treatment, it was not necessary to separate the prostate motion from the patient setup error. As mentioned in Sec. I, this strategy may not be effective for concurrent treatment of the prostate (a moving target) and pelvic lymph nodes (an immobile target). Nevertheless, for a fair comparison among the three different strategies, the isoshifting strategy in this paper only corrected for the prostate motion, not including the setup error.

II.C. MLC-shifting strategy

The MLC-shifting strategy is based on our previously proposed leaf-shifting algorithm,[16] which can follow the movement of the prostate while not significantly affecting dose distributions to the pelvic lymph nodes. Briefly, based on the magnitude and direction of the daily prostate movement, the algorithm was designed to adjust the positions of selected MLC leaf pairs to follow the translational motion of the prostate for each beam. The algorithm assumes that the prostate is a rigid body and the rotational motion is negligible. After shifting, the distance between the leaves in each shifted MLC pairs is kept the same as in the original plan. In other words, the portion of each MLC aperture that encompasses the prostate is translated to match the prostate position as determined by daily imaging, while the MLC leaves that expose radiation to the lymph nodes are not moved. Because the field size in unchanged and the changes in the off-axis factors contribute only a negligible change to the dose distribution,[16] a real time dose calculation is not required for this strategy. Currently, this strategy is not clinically feasible as it requires a new feature in the record and verify system to permit efficient adjustment of MLC leaf positions at the treatment console. Furthermore, logistic issues such as the pretreatment quality assurance have not been explored.

II.D. A special clinical case

A patient with high risk prostate cancer known to have nodal metastasis adjacent to a "horse-shoe" abdominal kidney was treated with the MAP strategy. The kidney was the major dose limiting organ for this patient. The kidney volume receiving more than 20 Gy (V20) was desired to be less than 15%. For this special case, an initial plan was designed to concurrently treat the prostate to 50 Gy and pelvic nodes to 45 Gy in 25 fractions, followed by a boost dose of 22 Gy to the prostate. For this patient, due to the special anatomy of abdominal kidney, the image guidance was initially altered to align to the pelvic bone to ensure the protection of the abdominal kidney while the planning margin to the prostate was enlarged to 1.0 cm (0.8 cm posteriorly). After eight treatments, the patient complained of rectal irritation; therefore, the subsequent treatment (17 fractions) was changed to MAP IMRT.

II.E. Dual image registration

To determine the prostate motion relative to the pelvic bone, two image registrations are needed using a single megavoltage cone beam CT (MV-CBCT) acquired prior to each treatment. The MV-CBCT was acquired with a total of 2 MU over 210° arc length using a commercial system (MVision™, Siemens Medical Solutions, Concord, CA). After MV-CBCT acquisition, two successive image registration procedures, one aligned to the pelvic bones and the other aligned to the implanted markers, were performed. The couch shifts from the bony alignment represent the setup error and were subsequently corrected by shifting the treatment couch. The prostate displacement relative to the pelvic bones was determined by the difference between the shifts of the two alignments. Based on the prostate position of the day, the IMRT plan in which the planned prostate position was best matched with the actual prostate position was chosen

TABLE I. MAP-IMRT plans and its clinical usage for 17 treatment days.

Plan type	Normal plan	Small posterior shifts	Large posterior shifts	Small superior shifts	Large superior shifts
Shifts	<0.3 cm [a]	0.4–0.7 cm	0.8–1.3 cm	0.4–0.7 cm	0.8–1.3 cm
Usage	6	1	0	7	3

[a]Shifts <0.3 cm in all directions or shifts dominantly in inferior or anterior directions.

according the criteria shown in Table I. If the prostate moved in two different directions, the direction with the larger shift was compensated. If the shifts in superior and posterior directions were the same, the superior shift was compensated.

II.F. Relative treatment dose comparison and analysis

With daily MV-CBCT, we calculated the delivered dose to the patient anatomy of the day. While we are under development to calibrate the CT density and to correct for the cupping effect of the MV-CBCT, we assigned a CT density of 1 g/cm^3 to all tissue. We also used the external contour of the planning CT to supplement the missing tissue (assigned to a CT density of 1 g/cm^3) due to the limited field of view with the current MV-CBCT acquisition system. With these approximations, the dose distributions calculated on MV-CBCTs were used for relative dose comparison with intended plans for this study.

Because of limited soft tissue contrast of low dose (2 MU/scan) MV-CBCT, directly contouring all organs of interest is challenging. For this study, we focused on the validation of the dose coverage of the two tumor targets and the dose to the kidney. Because of daily organ deformation, in addition to limited soft tissue contrast in MV-CBCT, the rectum and bladder were not included in the validation plans.

After rigid image registration of the pelvic bones, we transferred contours of the pelvic lymph nodes and the kidney from the planning CT to each daily MV-CBCT. Each MV-CBCT was input into the Pinnacle planning system as the primary image set and an in-house program was written to allow the selected contoured planning structures to be input with the planning CT (as the secondary image) into the Pinnacle system. Assuming a stationary relationship between the pelvic lymph nodes and the pelvic bones, the pelvic lymph nodal volume and the kidney were transferred from the planning CT to the MV-CBCT after a rigid body image fusion by aligning the pelvic bony structures. It should be noted that the breathing motion associated with the kidney is ignored in this study. The great challenge was to transfer the prostate contour. Once again, one could register the implanted markers between the daily MV-CBCT and planning CT to transfer the contour of the prostate. The image registration tool provided by the Pinnacle system automatically utilized translation and rotation transformation, but during the treatment only translational shifts were available. To fairly represent the treatment position of the prostate, the prostate contour from the planning CT was shifted according to the daily detected motion using an in-house program. The shifted contour, which represented the "prostate position of the day," was subsequently input into the corresponding MV-CBCT.

Three sets of validation plans were generated and compared. The first set of validation plans was created according to the MAP strategy; the second set was based on the isoshifting strategy; and the third set utilized the MLC-shifting method. For each MAP validation plan, the delivered plan of the day was directly applied to the corresponding MV-CBCT of the day. For each isoshift plan, the treatment isocenter was shifted according to the detected prostate displacement of the day and the MLC segments from the original plan were again applied to the MV-CBCT of the day with the shifted isocenter. In each MLC-shift plan, the affected MLC pairs in all segments from the original IMRT plan (the plan for unshifted prostate position) were shifted to track the prostate position of the day. The resultant dose distribution of each MLC-shift plan was calculated on the corresponding MV-CBCT of the day.

III. RESULTS

III.A. MAP-IMRT plans

A set of five individually optimized IMRT plans, referred to as MAP plans, was prepared and approved for the treatment of this patient. Table I lists the clinical usage of each plan over 17 treatment days. Figures 2(a) and 2(b) show the resultant dose volume histograms (DVHs) of the PTV, pelvic lymph nodes, small bowel, and kidney. The DVHs of the MAP plans were slightly different from each other because the optimal solution found by the computer optimizer was slightly different for each scenario.

III.B. Image guidance

Based on the 17 MV-CBCT acquired for this patient, the prostate moved 0.4–0.7 cm in the superior direction in 38% of treatment days, ≥ 0.8 cm superiorly in 19%, 0.4–0.7 cm posteriorly in 12%, and ≤ 0.3 cm in all directions in 31%. Seven of 17 days had a setup error ≥ 0.5 cm in any direction, while the remaining days had a setup error ≤ 0.5 cm in any direction. Setup errors ≥ 0.1 cm in any direction were corrected. Figure 3 shows the detected daily setup errors and the prostate movements along the three major axes. For this specific patient, the prostate movement was not random, shifting in the superior direction in more than 50% of the treatment days.

III.C. Dose validation with MV-CBCT

Figure 4(a) shows the details of the dose to 95% of the prostate ($D95$) calculated based on daily MV-CBCT. The $D95$'s of the MAP strategy were the delivered daily dose calculated based on the chosen plan of the day, compared to the $D95$ of the isoshifting and MLC-shifting methods. Since the MAP method only accounted for prostate movement in one direction, $D95 \geq 95\%$ of the prescription dose was only achieved on 11 of 17 days (65%). As expected, the isoshifting method followed the prostate movement and achieved $D95 \geq 95\%$ of the prescription dose for all 17 treatment days. Similarly, the MLC-shifting method also achieved $D95 \geq 95\%$ of the prescription dose in each of the 17 days. As noticed in Fig. 4(a), on the 15th treatment day, the detected prostate movements were 1.2 cm superior and 1.2 cm posterior, but only the superior shift was compensated by choosing the large superiorly shifted MAP-IMRT plan for the treatment. A similar situation occurred on the fifth treatment day.

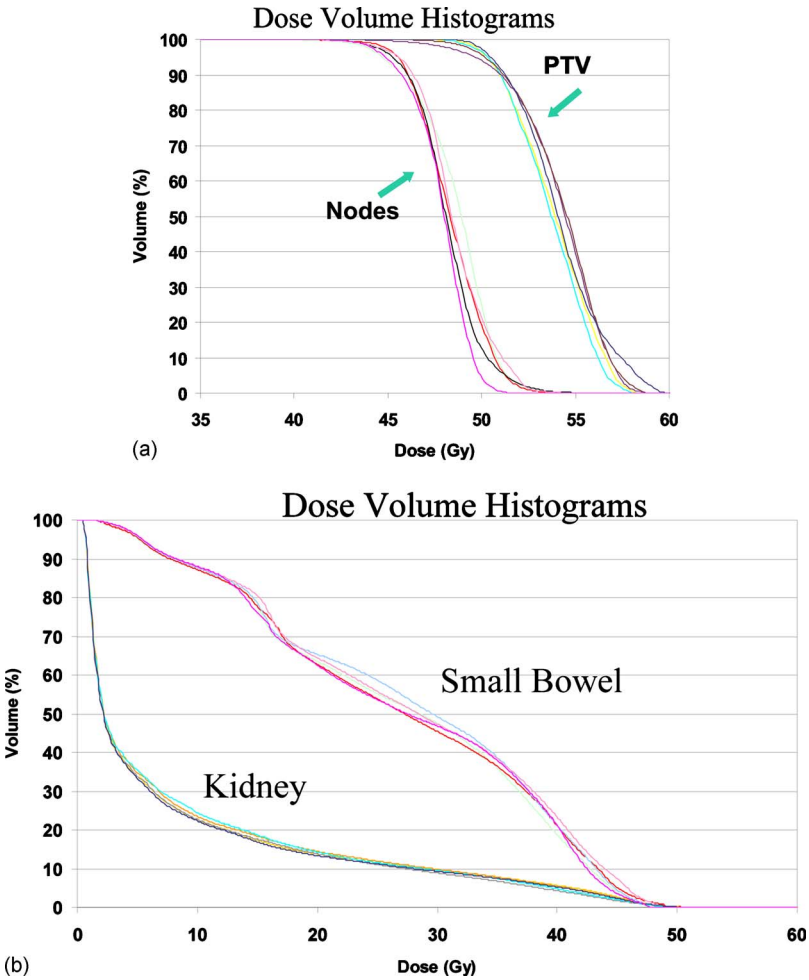

FIG. 2. (a) The dose volume histograms for the PTV and pelvic lymph nodes. (b) The DVHs for the small bowel and kidney.

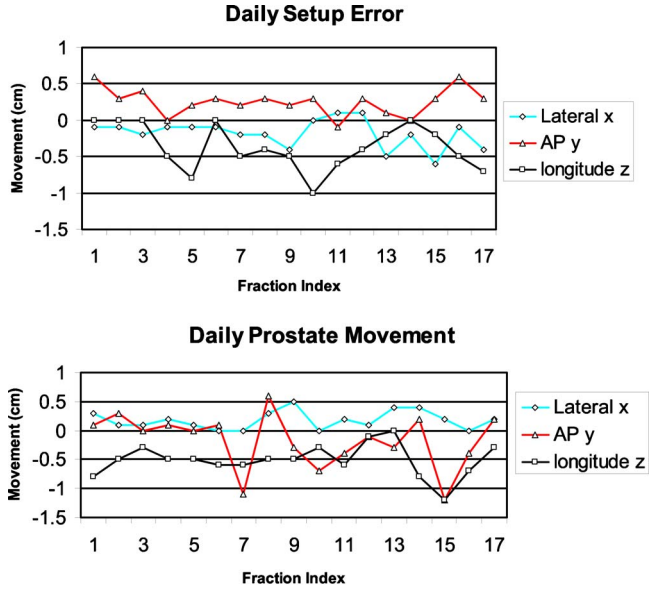

FIG. 3. The detected daily setup errors and the prostate movements along the three major axes for the 17 treatment days.

Figure 4(b) shows the dose to 95% of the pelvic lymph nodes ($D95$). The MAP-IMRT method achieved $D95 \geq 95\%$ of the prescription dose for all 17 days. The isoshifting method would have delivered $D95 \geq 95\%$ of the prescription dose in 13 of 17 days (76% of the treatment time), compared to 16 days (94% of the treatment time) in MLC-shifting method.

For the kidney, we used the end point of $V20$, the percentage volume receiving more than 20 Gy, to evaluate the three different strategies. With the MAP strategy, $V20$ of the kidney was $\leq 15\%$ for 13 of 17 days, as shown in Fig. 4(c). With the isoshifting method, $V20$ of the kidney was $\leq 15\%$ for only 2 of 17 days, compared to 14 of 17 days with MLC-shifting method. These results demonstrate that the MAP and MLC-shifting methods achieve better protection of the kidney than the isoshifting method.

IV. DISCUSSION

The current study describes our clinical experience in applying a new concept of multiple IMRT plans to accommodate independent movement of the prostate and pelvic lymph nodes under daily MV-CBCT image guidance. Although clinical implementation of this adaptive strategy at the current stage is still laborious and imperfect, this study provides a "proof of principle," describing a feasible planning, deliv-

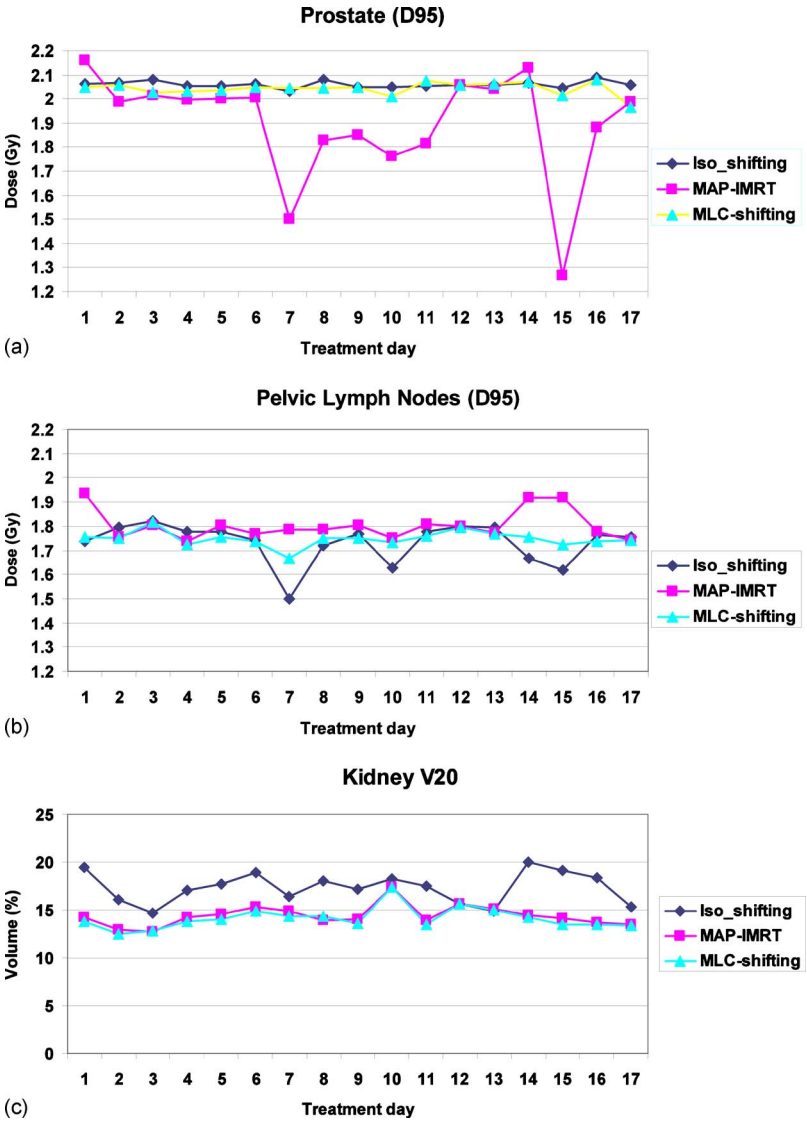

FIG. 4. (a) The dose to 95% of the prostate (*D*95) calculated based on daily MV-CBCT for the isoshifting, MAP-IMRT, and MLC-shifting strategies. (b) The dose to 95% of the pelvic lymph nodes (*D*95) calculated based on daily MV-CBCT for the three strategies. (c) The percentage volume receiving more than 20 Gy for the corresponding strategies.

ery, and verification process. For this particular patient, our primary goal of adequately treating the pelvic lymph nodes and prostate while protecting the kidney in the first phase of treatment was achieved. Because of the limited number of MAP IMRT plans in the pool for this early clinical implementation, only translational movement of the prostate in one direction was compensated. As shown in Fig. 4(a), this compensation was not sufficient when the prostate movement of the day was large in the superior and posterior directions, resulting in underdose of the prostate on these dates. Fortunately, the offline validation plans based on daily cone beam CT provided dose guidance for subsequent prostate boost treatments. This concept could be potentially extended to other pelvic, abdominal, and thoracic malignancies as well.

With advances in imaging technology and computer optimized treatment planning, we anticipated that it will be possible to acquire daily CT images and to develop an ideal strategy for real time replanning on a daily basis. Some researchers are already working to develop deformable image registration to improve the efficiency of structure delineation,[20–22] while others have sought to develop fast dose calculation engines and fast computer optimization algorithms.[23–25] For prostate only treatment, our clinical experience and other published studies[26,27] support that the isocenter shifting strategy is practical and effective. However, for concurrent treatment of the prostate and pelvic lymph nodes, this strategy may require a large planning margin for the pelvic lymph nodes, which may not be optimal if a small planning margin is desired, although a simulation study[15] showed that the problem of independent movement of the prostate and pelvic lymph nodes was negligible. It should be noted that this study was based on an assumption of a random movement of the prostate from the position at the planning CT and the validity of this assumption may need to be further investigated. Other studies[28–31] have demonstrated that prostate movement may not necessarily be random but depend on the shapes of the rectum and bladder during acquisition of the planning CT. The data from this study also show that the prostate position does not randomly displace from the position at CT simulation.

The MAP and MLC-shifting strategies investigated in this

study were not perfect and further improvement is necessary. Due to time and resource limitations, the MAP strategy can only anticipate a few presumed prostate positions. The planning process for five plans took about 1 day to complete. Quality assurance of these five plans took an additional 4 h to complete. In addition, a simple spread sheet (EXCEL and MICROSOFT OFFICE) was prepared to calculate the prostate movement relative to the pelvic bones. During each treatment, a physicist was present to help therapists to choose a proper plan. To create a relatively large number of MAP-IMRT plans without significantly increasing planning time, one could apply the MLC-shifting algorithm to create MAP plans for prostate motions in multiple directions provided that a fine MLC leaf width is available.

The clinical implementation of the MLC-shifting method requires a new feature in the record and verify system, which will allow users to adjust the MLC leaf positions at the treatment console in the near real time. As indicated in our study, this method can be considered as a simplified real time planning, without requiring contouring of each planning structures and fast dose calculation engines. With a finite MLC leaf width, the MLC-shifting strategy will have a limited resolution in the superior and inferior directions. Although a finer leaf width of 0.5 cm (rather than 1.0 cm used for this study) is commonly available, the impact of this limitation requires further investigations. Furthermore, other logistic issues, such as the pretreatment quality assurance process, decision of who should be responsible for shifting MLC leaf positions, etc., require further exploration.

One may consider other strategies to cope with the challenge of treating one moving target and one immobile target. One proposal is to prepare two plans: One for the pelvic lymph nodal volume and another for the prostate. If delivering the plans concurrently, overlap of the two plans when the prostate moved superiorly must be calculated on a day-to-day basis.[15] Similar to real time replanning, this requirement is not clinically feasible. If delivering these two plans sequentially, the treatment course can be significantly prolonged and the problem of overdose in the overlap region may still exist, albeit with a lower daily dose compared to concurrent delivery.

There are some limitations in this study. First, only an atypical patient was analyzed, although this special clinical scenario inspired us to conduct this research. Except for the abdominal kidney that imposed a small planning margin on the pelvic lymph nodal volume, the prostate and pelvic lymph nodal volumes of the patient are similar to the volumes of a typical patient. For a typical patient, one may consider the use of a larger margin either around the prostate or around the lymph nodes, or large margins on both targets. Larger planning margins, in general, are a suboptimal strategy, irradiating more normal tissue as a part of the targeting volume and resulting in increased normal tissue complications. The methodology of this study can be applied to other typical patients, but since the prostate motion is patient dependent, a study with more patients' data may not reach a different conclusion than the current study. For the same reason, the result of this study cannot be directly generalized to other patients.

Second, the MAP strategy only considers a few scenarios of possible prostate positions, not the actual prostate positions. By increasing the number of MAP plans in the pool, one can decrease the error associated with this strategy, but at the cost of significantly increased planning time, quality assurance, and decision making process during treatment. Third, due to the limitation of MV-CBCT, the validation plans could not include other organs of interest, such as the rectum and bladder. The validation plans can be applied to kilovoltage-CBCT, which may overcome the limitation of soft tissue contrast in MV-CBCT. In addition, the daily prostate contour was based on the implanted markers as a surrogate and rigidly transferred to the corresponding MV-CBCT, ignoring prostate rotation and deformation. Furthermore, the dose calculation in validation plans to verify the relative dose changes assumed a uniform tissue density. With a calibrated CT density table, it is possible to perform comparisons based on the absolute dose changes. However, because of the limited field of view (27 cm radius in an axial view) with our current MV-CBCT (Siemens Medical Solution), supplemental information from the planning CT for tissue outside the field of view[32] would still be required, which may complicate the dose calculation process.[33] Our future study will consider the use of KV-CBCTs, with which, we can further analyze the daily dose to the prostate based on the direct soft tissue contouring as well as the daily doses to the rectum and bladder.[34]

V. CONCLUSIONS

Although real time replanning may be the ideal strategy to accommodate independent movement of the prostate and pelvic lymph nodes during concurrent treatment, optimizing a set of IMRT plans with multiple prostate positions is an alternative strategy. The conventional isocenter shifting method is inadequate for selected cases where a small planning margin to both prostate and pelvic lymph nodal volumes is demanded. With an improved record and verification system, the MLC-shifting approach can further improve accommodation of prostate motion in the multiple directions, particularly with a fine MLC leaf width. Validation plans calculated with daily volumetric image guidance provide patient specific dosimetric monitoring and dose guidance, allowing us to adjust radiation dose in the boost phase of the treatment.

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